

**Evaluation of tolerability and antiepileptogenic efficacy of multitargeted drug combinations by a two-stage approach**

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# Multi-targeted drug combinations for antiepileptogenesis (“network pharmacology”)

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- For anti-epileptogenesis, rational drug combinations targeting multiple targets in an epileptogenic network (“network pharmacology”) may be more effective than treatment with single, highly specific drugs
  - (Löscher et al., *Nature Rev. Drug Discov.*, 2013)
- Clinical translation of such a network approach (which is tested in preclinical models) would benefit from repurposing of drugs that are clinically available
- W. Löscher’s group evaluates such novel multi-targeted drug combinations in WP02 of the EPITARGET consortium

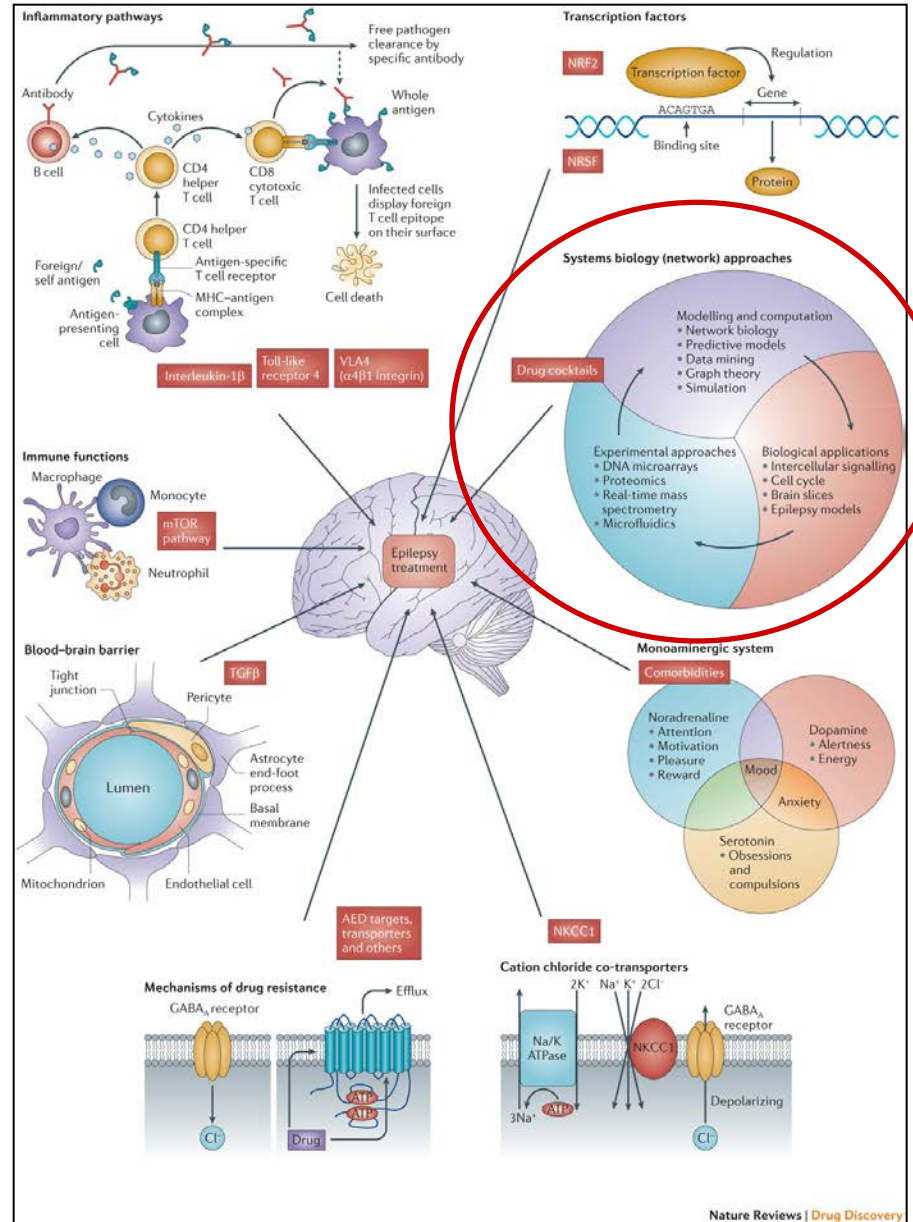
# Multi-targeted approaches to prevent epilepsy

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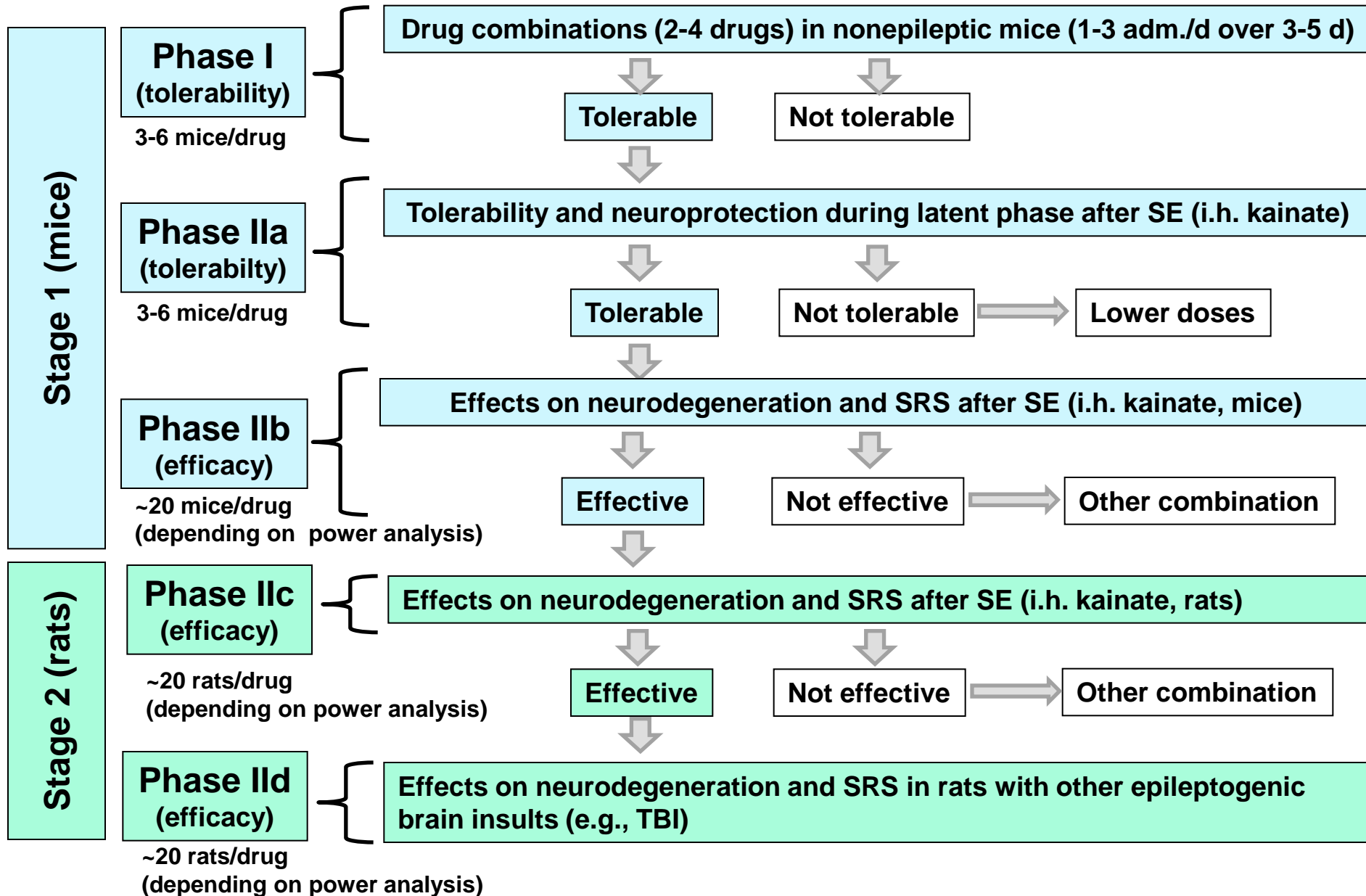
## New avenues for anti-epileptic drug discovery and development

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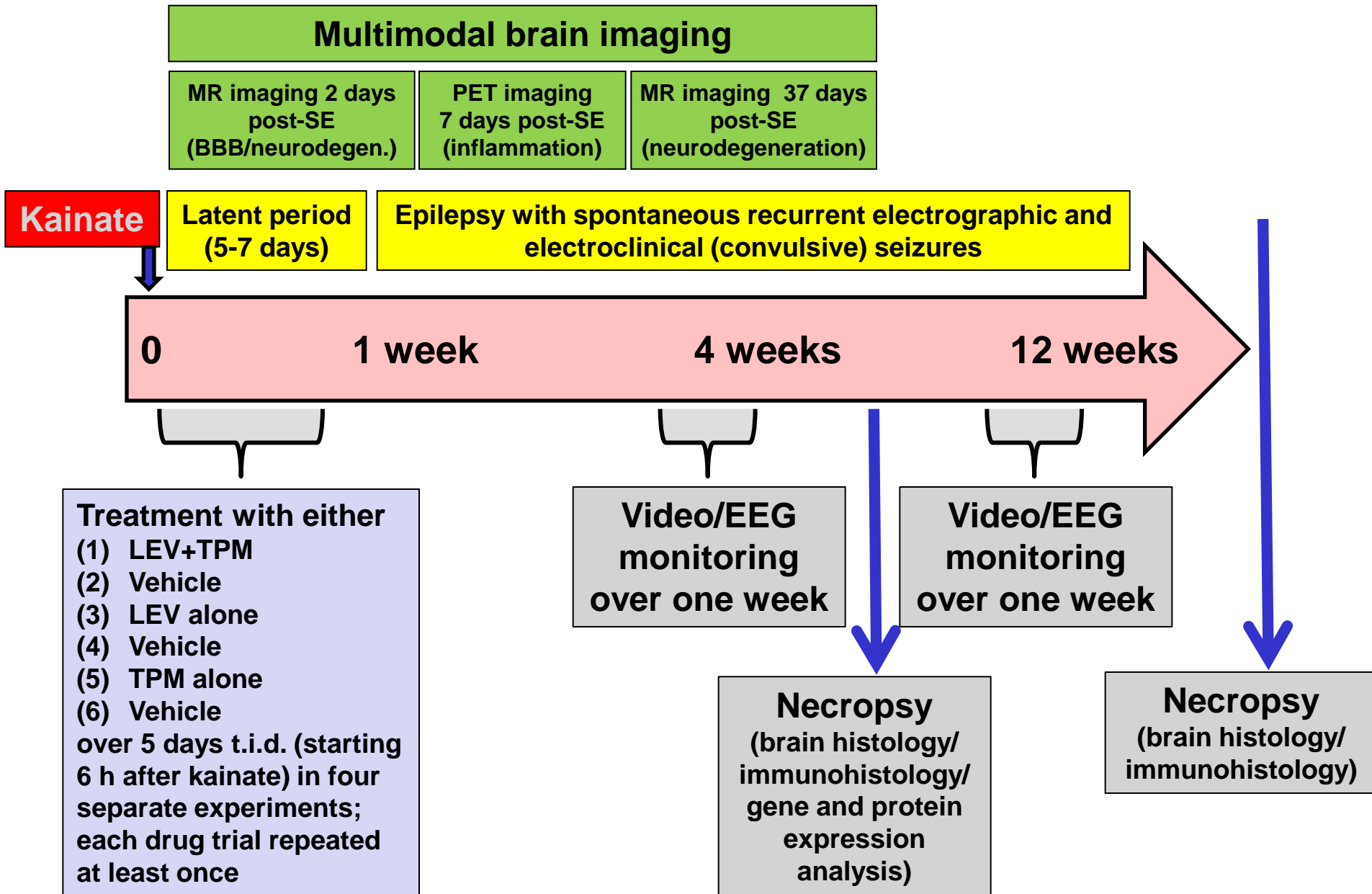




# Tolerability and efficacy testing of drug combinations in rodents (Two-stage approach)

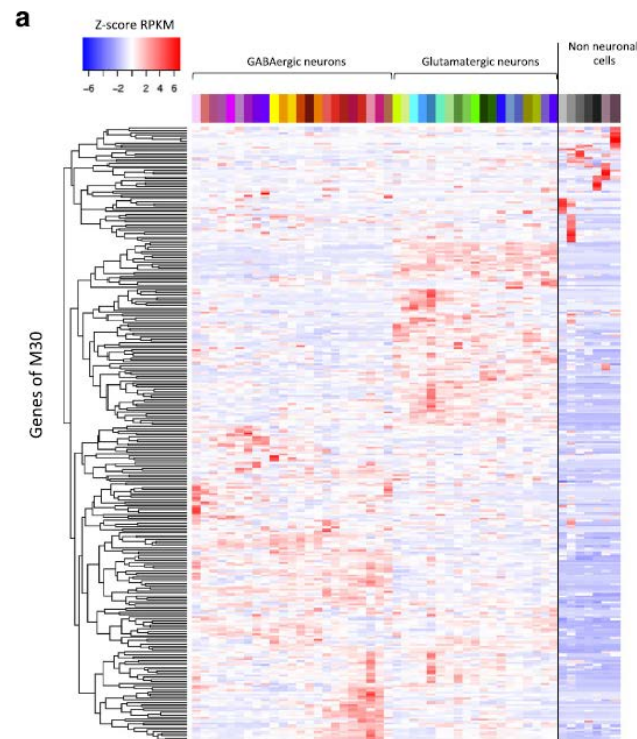


# Antiepileptogenic efficacy of levetiracetam and topiramate in mice



# Potential mechanisms of the favorable combination?

- No neuroprotective effect in the ih KA model in mice
- $\mu$ PET and  $\mu$ MRI imaging do not indicate any antiinflammatory, BBB-protective or neuroprotective effect of the LEV+TPM combination
- In a cooperation with Michael Johnson (Imperial College London), gene-regulatory network analysis is used to identify the potential therapeutic targets of the LEV+TPM combination in epileptic mice



# Challenges/bottlenecks

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- **Testing high numbers of drug combinations for antiepileptogenesis is extremely laborious and time-consuming**
- **The lack of reliable algorithms for EEG seizure detection adds to the problem**
- **As a consequence, testing of different doses per drug in a combination is hardly possible**
- **This may lead to false negative findings**

## Next steps to move forward

- **Continue drug combination testing by the two-stage approach**
- **Test most promising combination in a TBI model**



# Conclusions

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- **Using an algorithm based on clinical drug development, evaluation of various rationally chosen drug combinations in mice has identified an effective combination of two AEDs, levetiracetam and topiramate**
- **The disease-modifying mechanisms of this promising combination are currently being explored**
- **Based on our two-stage approach, the next step will be to study this combination in rats, preferably in a TBI model**
- **We expect that additional promising drug combinations will be identified soon**
- **All drugs are clinically approved, which should allow relatively rapid translation into clinical trials**

# The Hannover Epilepsy Research Team



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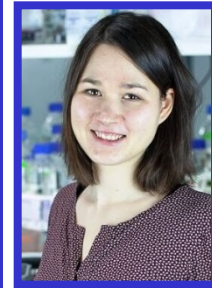
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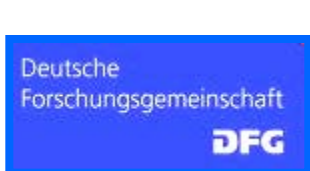


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**Thank you!**

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